

Applicants: Jingyue Ju et al.
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Accordingly, claims 74-92 are still pending and under examination.

Pursuant to the provisions of 37 C.F.R. §1.121, applicants annex hereto as **Exhibit A** a version of the amended claims marked up to show the changes made herein relative to the previous version thereof.

Obviousness-Type Double Patenting Rejection

In the October 9, 2002 Final Office Action, the Examiner stated that claims 74-92 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 6,046,005 in view of Arbo et al. (International Journal of Peptide and Protein Research, (1993), Vol. 42, pages 138-154). The Examiner stated that claims 1-22 of U.S. Patent No. 6,046,005 disclose the same method of instant claims 74-92, for sequencing DNA by detecting the identity of a dideoxynucleotide incorporated at the 3' end of a DNA sequencing fragment using mass spectrometry. The Examiner also stated that the basic steps of detection of DNA of the instant claims are the same as claims 1-2 of U.S. Patent No. 6,046,005, which comprises a) attaching a chemical moiety via a linker to a dideoxynucleotide, b) terminating a DNA sequencing reaction with a labeled dideoxynucleotide, c) capturing the labeled DNA sequencing fragment on a solid surface, d) washing the surface, e) freeing the DNA sequencing fragment from the surface, and f) analyzing the fragment using mass spectrometry so as to sequence the DNA.

The Examiner stated that claims 1-22 of U.S. Patent No. 6,046,005 do not teach a method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of

claim 74. The Examiner also stated that Arbo et al. teach a method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74 (Abstract and page 149, Column 2 to page 151, Column 1).

The Examiner stated that it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in the method of claims 1-22 of U.S. Patent No. 6,046,005, since Ju et al. state, "In such linkers, the linker will comprise a cleavable moiety that is either photo or chemically cleavable (Column 7, lines 1-3)." The Examiner also stated that by employing scientific reasoning, an ordinary practitioner would have been motivated to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in claims 1-22 of U.S. Patent No. 6,046,005, in order to achieve the express advantages, as noted by Ju et al., of linkers which will comprise a cleavable moiety that is either photo or chemically cleavable.

The Examiner stated that a timely filed terminal disclaimer in compliance with 37 C.F.R. §1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.130(b).

In response, applicants respectfully traverse the Examiner's rejection.

Applicants assert that the '005 patent in view of Arbo et al. do

not teach all the elements of the claimed invention. In particular, the cited references in combination do not teach the characteristics set forth in step (c) of amended claim 74. Thus, applicants' invention is not obvious over the '005 patent in view of Arbo et al. Accordingly, applicants request that the Examiner reconsider and withdraw this ground of rejection.

Rejection of Claims Under 35 U.S.C. §103(a)

The Examiner stated that claims 74-92 are rejected under 35 U.S.C. §103(a) as being anticipated by Ju et al. (U.S. Patent 6,046,005, issued April 4, 2000) in view of Arbo et al. (International Journal of Peptide and Protein Research, (1993), Vol. 42, pages 138-154).

The Examiner stated that Ju et al. teach a method for sequencing DNA by detecting the identity of a single or plurality of dideoxynucleotide incorporated to the 3' end of a DNA sequencing fragment using mass spectrometry (Abstract and Claims 1, 14, and 15, Figure 1 and Experimental Section), which comprises: a) attaching a chemical moiety via a linker to a dideoxynucleotide to produce a labeled dideoxynucleotide (Claims 1 and 15); b) terminating a DNA sequencing reaction with the labeled dideoxynucleotide to generate a labeled DNA sequencing fragment having a 3' end and the chemical moiety is attached via the linker to the 3' end of the DNA sequencing fragment (Claims 1 and 15 and Figure 1); c) capturing the labeled DNA sequencing fragment on a surface coated with a compound that specifically interacts with the chemical moiety attached via the linker to the DNA sequencing fragment, thereby capturing the DNA sequencing fragment (Claims 1 and 15); d) washing the surface to remove any non-bound component (Claims 1 and 15 and Experimental Section); e) freeing the DNA sequencing fragment from the surface by

disrupting and cleaving the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment and the compound on the surface (Claims 1 and 15 and Experimental Section and Figures 9-10); and f) analyzing the DNA sequencing fragment using mass spectrometry so as to sequence the DNA (Claim 14).

The Examiner stated that Ju et al. teach a method, wherein the interaction between the chemical moiety attached via the linker to the DNA sequencing fragment and the compound on the surface comprises a biotin-streptavidin interaction (Claims 19-20 and Experimental Section). The Examiner stated that Ju et al. teach a method, wherein the dideoxynucleotide comprises a cytosine or thymine with a 5-position and the linker is attached to the 5-position of cytosine or thymine (Figure 8 and Experimental Section). The Examiner stated that Ju et al. teach a method, wherein a plurality of different linkers is used to increase mass separation between different labeled DNA sequencing fragments and thereby increase mass spectrometry resolution (Column 7, lines 1-9 and column 9, lines 15-32). The Examiner stated that Ju et al. teach a method, wherein the interaction of the linker is cleaved by ultraviolet light (Figures 9-10). The Examiner also stated that Ju et al. teach a method, wherein the chemical moiety comprises biotin, the labeled dideoxynucleotide is a biotinylated dideoxynucleotide, and the surface is a streptavidin-coated magnetic bead solid surface (Figure 1 and Experimental Section and Claim 20). The Examiner stated that Ju et al. teach a method, wherein the biotinylated dideoxynucleotide is selected from ddATP-11-biotin, ddCTP-11-biotin and the compounds of claims 67-70 (Columns 6, lines 35-64 and Figures 8-10).

The Examiner stated that Ju et al. teach a method, wherein the steps (b) to (e) are performed in a plurality of connected

containers (Experimental Section). The Examiner stated that Ju et al teach method, wherein any linker comprises a photo or chemically cleavable moiety. The Examiner stated that Ju et al. do not teach a method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74. The Examiner stated that Arbo et al. teach method, wherein the cleavable linkers are a derivative of 4-aminomethyl benzoic acid containing fluorine of claim 74 (Abstract and page 149, Column 2 to page 151, Column 1). The Examiner also stated that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in the method of Ju et al., since Ju et al. state, "In such linkers, the linker will comprise a cleavable moiety that is either photo or chemically cleavable (Column 7, lines 1-3)." By employing scientific reasoning, according to the Examiner, an ordinary practitioner would have been motivated to combine and substitute the chemically equivalent cleavable linkers, which are a derivative of 4-aminomethyl benzoic acid containing fluorine of Arbo et al. in the method of Ju et al., in order to achieve the express advantages, as noted by Ju et al., of linkers which will comprise a cleavable moiety that is either photo or chemically cleavable.

In response, applicants respectfully traverse the Examiner's rejection.

Applicants again assert that the '005 patent in view of Arbo et al. does not teach all the elements of the claimed invention. In particular, the cited references in combination do not teach the characteristics set forth in step (c) of amended claim 74. Thus, the cited references cannot support a *prima facie* case of